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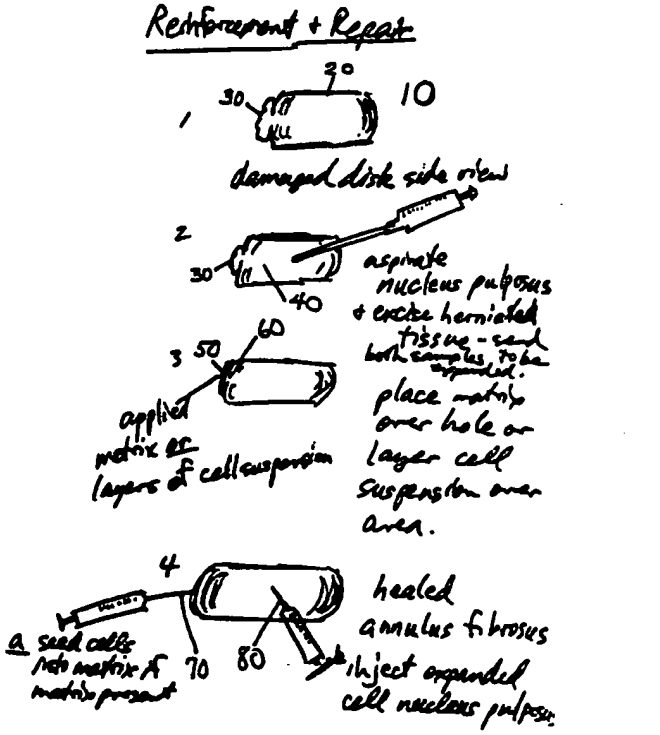
(54) Title: REPAIR OF INTERVERTEBRAL DISKS

(57) Abstract

This invention is a method of using a cell containing hydrogel suspension for treating a herniated intervertebral disk (10) by implanting a cell suspension into a patient, thereby forming a cell containing hydrogel adherent to at least one surface of the annulus fibrosus (20) of the herniated disk (10), wherein the cells are chondro–cyte, fibroblasts or osteoblast.



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REPAIR OF INTERVERTEBRAL DISKS

BACKGROUND OF THE INVENTION

Field of the Invention

This invention relates to the use of tissue engineering to repair a herniated disk, and more particularly, to the use of disaggregated chondrocytes with various matrix/delivery systems to perform such a repair.

Review of Related Art

An intervertebral disk is composed of an outer fibrous part (annulus fibrosus) that surrounds a central gelatinous mass (nucleus pulposus). Both tissues in the disk are chondrocytic in cell type. When a spinal disk injury occurs (herniated disk, see Figure 1), the disk reacts much like a tire with a bulge or blister. Over time the blister can become larger, leading to increased interior space for the nucleus pulposus. This in turn, decreases the ability of the disk to "cushion" the adjacent vertebrae. Depending on the location of the herniation, the bulge may put pressure on the spinal cord which results in pain, reduced mobility and other complications.

Current treatment modalities include two major surgical interventions: the removal of the disk and fusion. Both of these procedures lead to limitation in spinal motion. In some cases, a prosthetic disk is placed in the

intervertebral space. However, problems with these devices include poor biocompatibility of the device material, improper placement, or surgical complications of the procedure. Thus, there is a need for an improved method for treating herniation of intervertebral disks.

SUMMARY OF THE INVENTION

It is an object of this invention to provide a minimally invasive technique to repair a herniated disk rather than remove it altogether. This and other objects of this invention are provided in one or more of the following embodiments.

In one embodiment, this invention provides a method for treating a ruptured intervertebral disk by aspirating all or part of a cell-containing gel from the disk, thereby reducing the nucleus pulposus volume; excising damaged tissue from the annulus fibrosus of the ruptured disk leaving a hole therein; covering the hole with a layer containing cells, said cells being attached to a porous matrix comprising a crosslinked biocompatible polymer; and injecting a cell-containing suspension into the disk through the annulus fibrosus to restore the nucleus pulposus volume. In a preferred embodiment, the cell-containing suspension is obtained by collecting a population of chondrocytic cells from the

annulus fibrosus or the nucleus pulposus, and expanding the population of chondrocytic cells.

In another embodiment, this invention provides a method for treating a herniated intervertebral disk by applying over the damaged area of the disk, a layer containing cells and a biocompatible polymer which is crosslinked to form a porous matrix.

In yet another embodiment, this invention provides a method for preparation of a suspension of chondrocytes suitable for injection into a vertebral disk by expanding a population of chondrocytes obtained by aspirating a portion of an intervertebral disk; and mixing the expanded population of chondrocytes with a biocompatible polymer to form a suspension of chondrocytes suitable for *in vivo* application onto the exterior wall of an intervertebral disk where the suspension forms a cell-containing hydrogel when implanted into the body of a patient.

In still another embodiment, this invention provides a method for applying a suspension of chondrocytes to the surface of a herniated disk for repair of the disk by mixing a population of chondrocytes with a biocompatible polymer to form a suspension of chondrocytes that will form a cell-containing hydrogel when implanted into the body of a

patient; and applying the suspension to the surface of a herniated disk to form one or more layers of cell-containing hydrogel adherent to the exterior wall of the disk.

In yet another embodiment, this invention provides a method for injecting a suspension of chondrocytes into a herniated disk for repair of the disk, the method comprising the steps of mixing a population of chondrocytes with a biocompatible polymer to form a suspension of chondrocytes; and injecting the suspension into a herniated disk where the suspension forms a cell-containing hydrogel in the disk.

In still another embodiment, this invention provides a method of using a cell-containing hydrogel suspension for treating a herniated intervertebral disk by implanting a cell suspension into a patient having a herniated disk, thereby forming a cell-containing hydrogel adherent to at least one surface of the annulus fibrosus of the herniated disk. Preferably the cells are chondrocytes, fibroblasts or osteoblasts.

In the method of this invention, disaggregated chondrocytes, fibroblasts or osteoblasts are suspended in a hydrogel or other liquid/semiliquid carrier and painted, brushed, sprayed, or applied by other means in a layer or layers to the exterior wall of the intervertebral disk to

strengthen the wall construct or create replacement wall, and optionally similarly suspended cells may be introduced into the interior of the disk as well. A primary difference between the method of this invention and the methods in use prior to this invention is that this method of repair allows for the original tissue to remain in place rather than replacing it with a synthetic material. Potential advantages of the present invention include better spinal motion, less degeneration of surrounding area, shorter recovery time, and overall improved results when compared to diskectomy, fusion or implantation of a prosthetic disk.

BRIEF DESCRIPTION OF THE FIGURES

Figure 1 shows an portion of the spinal column having a herniated disk between two vertebrae.

Figure 2 is a schematic representation of the steps in the method for repair of a herniated disk.

Figure 3 is a schematic representation of the steps in the method for strengthening the annulus fibrosus.

DETAILED DESCRIPTION OF THE EMBODIMENTS

This invention utilizes a minimally invasive technique to repair a

herniated disk rather than remove it altogether as is the current standard of care. Disaggregated chondrocytes, fibroblasts or osteoblasts are suspended in a hydrogel or other liquid/semiliquid carrier and painted, brushed, sprayed, or applied by other means in a layer or layers to the exterior wall of the intervertebral disk. This method can reinforce the annulus fibrosus in the case of a minor herniation or can be used as a "patch" when the herniated tissue is removed. Either application should prevent further damage and/or rupture and may lead to the restoration of full disk function.

Cell/Matrix Compositions

According to this invention, herniated disks are repaired using materials made up of cells dispersed in a matrix. The cell-containing matrix adheres to the disk. The cells may be suspended in a liquid/semiliquid carrier which is applied to the disk and then hardens into a cell-containing matrix. Alternatively, material which forms the matrix may be applied to the disk, and the matrix subsequently seeded with cells. The matrix material may be applied in the fluid state to conform to the shape of the disk surface and then cure, crosslink or harden to form the matrix, or the matrix may be formed first and then applied to the surface of the disk.

The matrix material is biocompatible and forms a porous matrix under

physiological conditions, typically by cross-linking of biocompatible polymers. The polymers may be natural or synthetic, biodegradable or non-biodegradable, and the polymer(s) may be further modified for enhanced properties. Typical materials for the matrix are described in European Patent No. 0 299 010 or in International Patent Publication No. WO 94/25080, both of which are incorporated herein by reference. In one preferred mode, the matrix is a hydrogel, but use of other materials which form a porous, fibrous network that can contain cells is also within the contemplation of this invention. Suitable raw materials which may be used to produce the hydrogel in which the cells are suspended include sodium alginate, which has been tested with chondrocytes, as well as PLURONICS™ and TETRONICS™.

Procedures for preparing the matrices and seeding them with cells are described in these publications, and the skilled worker will readily adapt those procedures to this invention in view of the guidance provided herein. The hydrogel-cell suspension may be prepared as described for products used in treatment for vesicoureteral reflux using autologous auricular chondrocytes in sodium alginate. Alternatively, the hydrogel-cell suspension may be prepared as described in International Patent Publication No. WO 97/17038, by Vacanti, et al., entitled "Hydrogel-cell composition - for generating new tissue on surface of structure or organ," incorporated herein by reference. Other cell-

containing suspensions which can be "painted" on physiological surfaces in an equivalent manner to the hydrogel-cell suspension described herein may also be used to repair intervertebral disks according to this invention.

The cells in the matrix may be any suitable cell type, but preferably the cells will be derived from the structure to be repaired (i.e., cells from the herniated disk, or cells of the same cell type, will be used). Typically the cells are chondrocytes, although osteoblasts or fibroblasts may be used. Chondrocytes may be obtained from any cartilaginous tissue in the patient, or may be allogeneic chondrocytes, so long as care is taken to mitigate any adverse reactions to the allogeneic cells. Alternatively, other cell types known in the field of tissue engineering to proliferate on the matrix of this invention may be used in this method.

Cells obtained for use in the matrix may be used directly or expanded by culture under suitable conditions. Standard cell culture conditions may be used, taking into account that results of this cell expansion process must be suitable for re-introduction into the patient. The cell suspension may contain additives, such as growth factors, colony stimulating factors, cytokines, adhesion peptides, antibiotics, cell nutrients, physiologically compatible buffers and salts, and the like. The components of the cell suspension may be combined using any procedure which preserves viability of a substantial

portion of the cells (typically 35% of the cells, preferably at least 50%). Such procedures are known to those skilled in the art of tissue engineering, and suitable procedures are described in the patent publications incorporated herein by reference.

Treatment Modalities

This invention is directed to the repair of intervertebral disks. Defect(s) which may be overcome by the method of this invention include damage of, abnormal development of, weakness of, or missing sections of exterior or outer intervertebral disk wall. This method may be used for repair of spinal/skeletal injuries by augmenting existing tissue which would result in increased strength, improved or restored function, or providing a bridge for missing sections. In a preferred embodiment, the method of this invention is used as a first step/additional treatment in combination with spinal cord pain management/reconstruction by removing fluid from inside the disk thus reducing pressure on the outer wall of the disk. The cells in the fluid may then be expanded *in vitro* and re-implanted once the disk wall has been strengthened by application of the cell-matrix structure according to this invention.

The method described herein can be performed in open surgery or

endoscopically. A typical procedure is illustrated in Figure 2. Figure 2-1 shows a side view of herniated disk **10** in which the wall (annulus fibrosus **20**) has a damaged section **30**. Figure 2-2 shows the first step in the repair procedure. Herniated tissue **30** is removed. Usually, a small fragment of undamaged annulus fibrosus will be taken at the same time and sent to a cell culture facility for isolation and expansion of the cell population. After cell expansion, a second procedure would seed cells into the interior of the disk and/or onto the matrix. Preferably, all or a part of the nucleus pulposus (**40**) of herniated disk **10** is aspirated. Removal of part of nucleus pulposus **40** relieves the pressure on the ruptured wall and/or the patch placed over the rupture as described in the following paragraph. The aspirated material may be stored for later re-introduction into the interior of the disk; any method of cell storage which maintains adequate viability for future use is within the contemplation of this invention. Alternatively, the cell population contained in the aspirate may be expanded.

As shown in Figure 2-3, a matrix "patch" **50** is placed over the resulting hole **60** in the annulus fibrosus. Patch **50** may be formed from a fluid composition containing a polymer that will harden when in contact with biological tissue to form a porous matrix, or it may be a preformed layer of fibrous material that can be applied to the exterior disk wall. A preformed

porous patch applied during an open surgical procedure may be sutured in place, or fibrin glue may be used to secure the patch in either endoscopic or open surgery. The fluid composition may contain cells in suspension, or cells may be seeded **70** onto the matrix once it has formed (See Figure 2-4).

After hole **60** in the annulus fibrosus has been closed, the volume of the nucleus pulposus is preferably restored by injection **80** of stored aspirate or a cell suspension, which preferably contains expanded cells described above, and more preferably, contains material that will have fluid consistency similar to the original nucleus pulposus, e.g., polymers that crosslink under physiological conditions to form a hydrogel with the desired properties. Suitable procedures for injecting material for volume restoration are analogous to the surgical procedures for introducing and removing arterial catheters.

In a alternative embodiment (shown in Figure 3), minor herniated tissue can be strengthened with layers of the cell suspension as needed. Disk **15** in Figure 3-1 has a minor herniation which weakens the wall (**25**) without significantly changing the volume of disk **15**. As shown in Figure 3-2, annulus fibrosus **25** may be strengthened by applying a layer (**55**) over damaged section **35** which is a fibrous matrix containing cells. Preferably, the layer is applied as a cell-containing suspension which is painted, sprayed or brushed on an area corresponding to at least damaged section **35** of the exterior

disk wall. Suitable procedures for preparation of such a cell suspension as well as procedures that may be adapted for applying the suspension to the disk wall are described in International Patent Publication No. WO 97/17038.

Treatment according to this invention may optionally include administration of drugs and/or other biological materials as appropriate. For example, one or more antibiotics, one or more growth factors for maintenance or stimulation of the cells, or nutrient medium components to support cell viability may be included in the cell suspension. Alternatively, such components may be administered separately, preferably by direct application in the region of the disk. Preferably, local administration of antibiotics is included in the method to reduce the risk of infection in the procedure. Where the cell suspension contains allogeneic cells or other foreign immunogenic material, immunosuppressive drugs may also be included.

Work reported by Ashton and Eisenstein in Spine, Feb 15, 1996, pages 421-426, states that the neuropeptide, Substance P had a small stimulatory effect on disk cell proliferation in vitro. Their conclusion is that further investigation is required to establish if Substance P has a biologic relevance to the maintenance or repair of the intervertebral disk. Substance P may be used according to this invention to help in the expansion and growth of cells used in the procedure. Application of Substance P for cell expansion *in vitro* may use

conditions analogous to those described by Ashton and Eisenstein. Suitable conditions for use of Substance P *in vivo* will be readily determined by the skilled clinician in view of the disclosures of Ashton and Eisenstein.

For purposes of clarity of understanding, the foregoing invention has been described in some detail by way of illustration and example in conjunction with specific embodiments, although other aspects, advantages and modifications will be apparent to those skilled in the art to which the invention pertains. The foregoing description and examples are intended to illustrate, but not limit the scope of the invention. Modifications of the above-described modes for carrying out the invention that are apparent to persons of skill in the art of tissue engineering, medicine, and surgery, and/or related fields are intended to be within the scope of the invention, which is limited only by the appended claims.

All publications and patent applications mentioned in this specification are indicative of the level of skill of those skilled in the art to which this invention pertains. All publications and patent applications are herein incorporated by reference to the same extent as if each individual publication or patent application was specifically and individually indicated to be incorporated by reference.

Claims:

1. A method of using a cell-containing hydrogel suspension for treating a herniated intervertebral disk, said method comprising:

implanting a cell suspension into a patient having a herniated disk, thereby forming a cell-containing hydrogel adherent to at least one surface of the annulus fibrosus of the herniated disk,

wherein the cells are chondrocytes, fibroblasts or osteoblasts.

2. A method for applying a suspension of chondrocytes to the surface of a herniated disk for repair thereof, said method comprising:

mixing a population of chondrocytes with a biocompatible polymer to form a suspension of chondrocytes, said suspension forming a cell-containing hydrogel when implanted into the body of a patient; and

applying the suspension to the surface of a herniated disk to form one or more layers of cell-containing hydrogel adherent to the exterior wall of the disk.

3. A method for injecting a suspension of chondrocytes into a herniated disk for repair thereof, said method comprising:

mixing a population of chondrocytes with a biocompatible polymer to form a suspension of chondrocytes; and

injecting the suspension into a herniated disk,

wherein the suspension forms a cell-containing hydrogel in the disk.

4. A method for preparation of a suspension of chondrocytes suitable for injection into a vertebral disk, said method comprising

expanding a population of chondrocytes obtained by aspirating a portion of an intervertebral disk; and

mixing the expanded population of chondrocytes with a biocompatible polymer to form a suspension of chondrocytes, said suspension forming a cell-

containing hydrogel when implanted into the body of a patient,

wherein the suspension is suitable for *in vivo* application onto the exterior wall of an intervertebral disk.

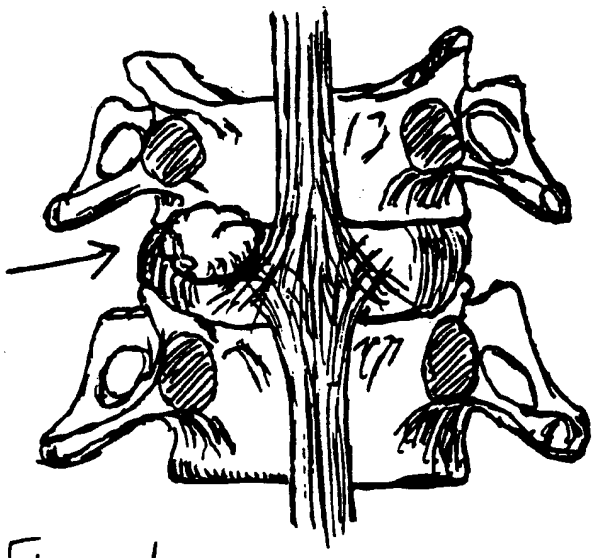


Figure 1
Herniated Disk

Figure 2
Reinforcement + Repair

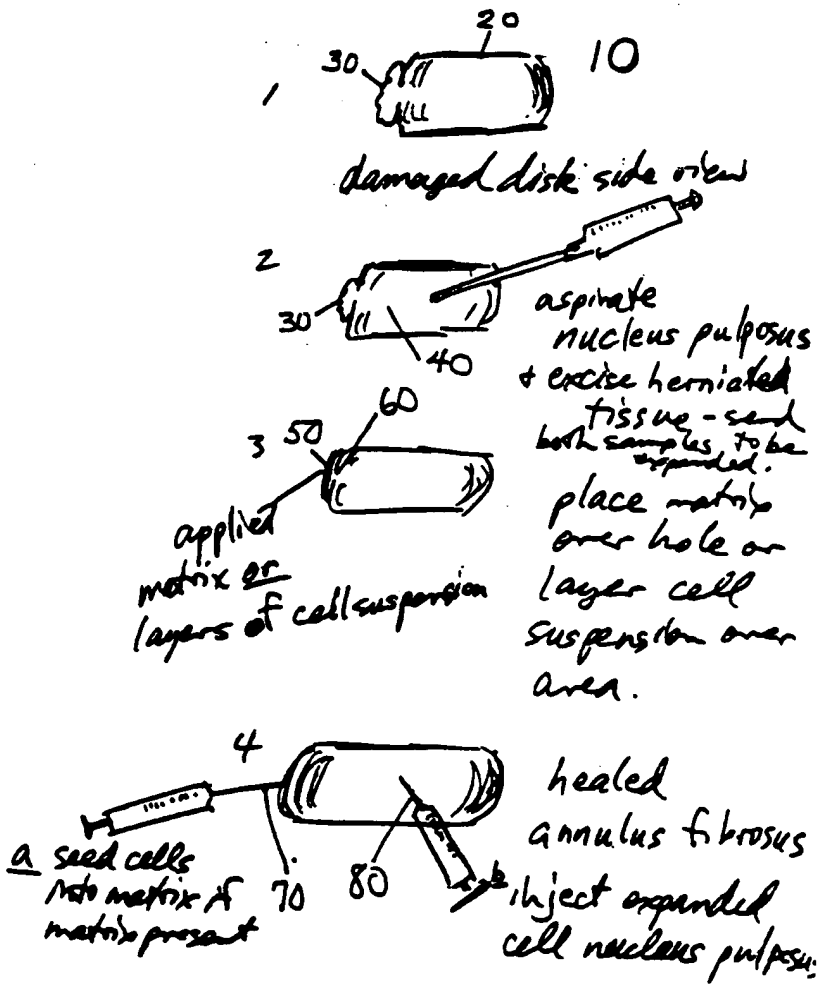
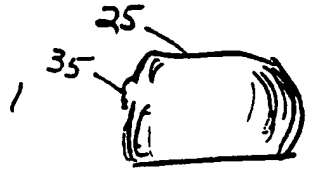


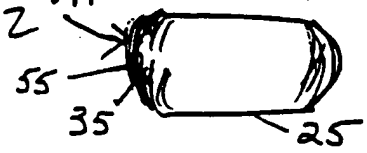
Figure 3

Strengthening Annulus fibrosus



damaged disk side view

applied cell/suspension via painting, spraying or brushed on



INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/14380

A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) :A61B 19/00
US CL :128/898; 424/422; 623/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 128/898; 623/11, 16, 17, 66, 901; 424/422, 423, 426

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS, DIALOG, MEDLINE, ISR

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P	US 5,709,854 A (GRIFFITH-CIMA et al.) 20 January 1998, entire document.	1-4
X,P	US 5,723,331 A (TUBO et al.) 3 March 1998, entire document.	1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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